PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 209737/CMH	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/01650	International filing date *(day/month/year)* 16.04.2003	Priority date *(day/month/year)* 17.04.2002
International Patent Classification (IPC) or both national classification and IPC C12N5/06		
Applicant BROWN, Jason, Peter et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.11.2003	13.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vix, O Telephone No. +49 89 2399-7326

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/01650

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-70 as originally filed

Claims, Numbers

1-35 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 30,32-33

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 30,32-33

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-29,31,34-35
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-29,31,34-35
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	see comments

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: THEISEN MANFRED ET AL: "Trans-immortalization strategies in transgenics." 1995, STRATEGIES IN TRANSGENIC ANIMAL SCIENCE., PAGE(S) 311-324 , AMERICAN SOCIETY FOR MICROBIOLOGY (ASM) BOOKS DIVISION, 1325 MASSACHUSETTS AVE. NW, WASHINGTON, DC 20005-4171, USA

D2: PAVIRANI A ET AL: "RECOMBINANT PROTEINS OF THERAPEUTIC INTEREST EXPRESSED BY LYMPHOID CELL LINES DERIVED FROM TRANSGENIC MICE" BIO/TECHNOLOGY, NATURE PUBLISHING CO. NEW YORK, US, vol. 7, no. 10, 1 October 1989 (1989-10-01), pg 1049-1054

D3: KNOTT CHRISTINE L ET AL: "Evaluation of Bcl-2/B cell transgenic mice (B6) for hybridoma production." HYBRIDOMA, vol. 15, no. 5, 1996, pages 365-371,

D4: WO 99/45962 A (BALL WILLIAM J JR ;FISHWILD DIANNE M (US); GENPHARM INT (US); LONB) 16 September 1999 (1999-09-16)

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty (Art. 33(2) PCT)

The application discloses method for the isolation of clonal cell lines secreting an antibody of choice from a transgenic mouse and consecutive production of monoclonal antibodies without the requirement for fusing antibody secreting cells with myelomas to produce hybridomas. In particular, it relates to a method using antibody secreting cells from an animal, which cells are capable of changing from a non-immortalised state in absence of a stimulus to immortalised state after exposing them to the stimulus following their extraction from the animal.

The different steps of the claimed method appear to be new in view of the available prior art since it provides a multi-step method allowing antibody expression from selected cell-lines without using the common hybridoma fusion strategy (e.g. as seen in D3-D4).

2. Inventive step (Art. 33(3) PCT)

Common technologies were available in the field of monoclonal antibody production using transgenic animals (e.g. see D3-D4) for the production of immortalised antibody secreting cells. These methods teach the fusion of antibody secreting B-cells with myeloma cells which achieve a low frequency of immortalisation (see D3).
In view of this closest prior art D3/D4, the technical problem to be solved by the present invention may be regarded as the provision of a method to improve the immortalisation efficiency in order to increase the diversity of the antibody secreting cells.

The solution to this problem proposed in claims 1-29 (immortalisation of antibody secreting cells by means of one or more transgenes present in the cells) of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

D2 describes a method for *onc*- or *myc*-mediated immortalization in vitro of transgenic lymphocytes to produce cell types for the expression of proteins. This takes place in cell lines derived from T-cells which can not be used for antibodies production. Moreover, in D1 and D2 the oncogenes are constitutively expressed in the lymphoid tissues, whereas in the application, the transgenes will only result in immortalisation in response to a stimulus, which presents the advantage of permitting immortalisation of antibody secreting cells ex vivo, thereby reducing the suffering of the animal.

Thus, in absence of a clear incentive to combine the existing technical teaching shown in D3-D4 (immortalised antibody secreting cells) and D1-D2 (protein expression system in a *onc*- or *myc*- mediated immortalised lymphoid cell lines) with an inducible expression system, the presence of an inventive step can be acknowledged for the subject-matter of claims 1-29, 31 and 34-35.
Thus these claims do meet the requirements of Article 33(3) PCT.

3. Industrial applicability

For the assessment of the present claim 1-29 (which relate to a method for producing antibody-producing cells and comprising an extraction step from an animal) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. Consequently, under the provision of Rule 67.1(iv) PCT, no statement with regard to industrial applicability of said claims (and the derived cells or antibodies and their use: claims 30-35) will be made (Article 34(4)(a)(I) PCT).